

The Diverse Clinical Features of Chromosome 22q11.2 Deletion Syndrome (DiGeorge Syndrome)

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A 2-year-old boy with chromosome 22q11.2 deletion syndrome was referred for recurrent sinopulmonary infections. He was diagnosed shortly after birth by a fluorescence in situ hybridization test that was performed due to interrupted aortic arch type B. He had no hypocalcemia, and his recovery from cardiac repair was uneventful. He had difficulty feeding and gained weight slowly, but, otherwise, there were no concerns during his first year of life. At 15 months of age, he began to develop significant otitis media and bronchitis. He was hospitalized once for pneumonia at 18 months of age and has never been off antibiotics for more than 1 week since then. He has not had any previous immunologic evaluation.

Recurrent sinopulmonary infections in a child with chromosome 22q11.2 deletion syndrome can have the same etiologies as in any other child. Atopy, anatomic issues, cystic fibrosis, and new environmental exposures could be considered in this setting. Early childhood can be problematic for patients with chromosome 22q11.2 deletion syndrome due to unfavorable drainage of the middle ear and sinuses. Atopy occurs at a higher frequency in 22q11.2 deletion syndrome, and these children also have a higher rate of gastroesophageal reflux and aspiration than the general population. As would be appropriate for any child who presents with recurrent infections at 2 years of age, an immunologic evaluation should be performed. In this review, we will highlight recent findings and new data on the management of children and adults with chromosome 22q11.2 deletion syndrome. © 2013 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2013;1:589-94)

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The estimated prevalence for chromosome 22q11.2 deletion syndrome is 1 in 4000 births.^{1,2} This is a haplosufficiency disorder, and, therefore, the chance of an affected parent having

an affected child is approximately 50%. For this reason, it is anticipated that the prevalence of chromosome 22q11.2 deletion syndrome will rise. Spontaneous or *de novo* mutations account for the majority, or approximately 90%, of 22q11.2 deletions; only approximately 10% are inherited from an affected parent.³ Given the high frequency of this condition, the multidisciplinary needs, and the high rate of immunodeficiency and allergy, it often occurs that allergists and immunologists are asked to supervise and coordinate the care of patients with chromosome 22q11.2 deletion syndrome. In this review article, we will review the associated clinical features as well as our current understanding of the immune deficiency in this syndrome.

The diagnosis of chromosome 22q11.2 deletion syndrome often follows the identification of the congenital cardiac anomaly, as was the case in the vignette presented earlier. Although 20% of patients will not have a cardiac anomaly, this remains the most common reason for referral for genetic testing. The most commonly used diagnostic test is fluorescence in situ hybridization, which has a strong track record but is slow and expensive. Today, 2 other diagnostic tests are vying to supplant the traditional fluorescence in situ hybridization assay. A PCR-based technology (multiplex ligation-dependent probe amplification) is widely used in Europe and is becoming more accepted in the United States.⁴ As a PCR-based assay, the turnaround time is rapid, and the cost is much lower. The second test is the single nucleotide polymorphism (SNP) array. Although the SNP array is more expensive than fluorescence in situ hybridization, it has the advantage of being able to identify atypical deletions as well as alternative explanations for the phenotype. However, because copy number variations are common, it is necessary to exercise caution when interpreting the findings of SNP arrays.

The decision to test for 22q11.2 deletion syndrome is often straightforward, such as when multiple defects and/or symptoms commonly seen in the syndrome are present simultaneously. In other cases, this is not as clear. Clinicians should apply their clinical judgment individually for each case; however, in certain settings, we think that testing is generally advisable. These settings include cardiac defects when associated with any other defect listed in Table I, speech delay associated with any other defect in Table I, and, finally, hypocalcemia with or without other obvious defects. Importantly, as seen in Table I, cardiac defects, immune deficiency, hypocalcemia, and velopharyngeal insufficiency are the most common defects being seen in patients with 22q11.2 deletion syndrome. In addition, screening is indicated when a parent is affected and also when there is an affected sibling, even if parents are genotypically normal. In 2005, a study of 100 children with 22q11.2 deletion syndrome in Sweden found that the most common clinical features that lead to diagnosis in children younger than 2 years of age were cardiac defects, absent or hypoplastic thymus, hypocalcemia, and characteristic dysmorphic features. In children older than 2 years

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Abbreviations used*HIV*- Human immunodeficiency virus*HLA*- Human leukocyte antigen*Ig*- Immunoglobulin*PCR*- Polymerase chain reaction*SNP*- Single nucleotide polymorphism

of age, the features that led to a diagnosis were most often cardiac defects, recurrent infections, speech delay, developmental delay, and characteristic dysmorphic features.⁵

Once a patient has been identified as having chromosome 22q11.2 deletion syndrome, a multidisciplinary approach should be engaged to ensure that the patient has all of his or her complex needs identified. The major phenotypic features seen in the syndrome are listed in Table I.⁶ It may be appreciated that the syndrome crosses all organ systems, and, indeed, the clinical heterogeneity represents a significant barrier for patients to receive appropriate care. There are not many centers that can offer dedicated subspecialists for each of the affected organ systems. In addition to each of the relatively common features, a number of other findings that are less clinically significant or less common are also listed in Table I.⁷ In the following paragraphs, we briefly review some of the key phenotypic features that impact directly on the care of patients with chromosome 22q11.2 deletion syndrome, particularly from the perspective of allergy and immunology.

KEY PHENOTYPIC FEATURES

The cardiac defects are generally apparent shortly after birth, and the repair of these anomalies is usually the most significant aspect of clinical care in the first few weeks of life.⁵ Another feature that can present in the first 1 or 2 weeks of life is hypocalcemia. Chromosome 22q11.2 deletion syndrome is the most common cause of congenital hypoparathyroidism, and prompt attention to the calcium levels as well as vitamin D replacement is warranted. Although conotruncal cardiac anomalies and hypoparathyroidism are often the features that bring the patient to attention, these are not often the conditions for which the allergist/immunologist will become involved.

One of the major contributions to recurrent infections in these children is the palatal dysfunction. The majority of patients will have palatal weakness, and a minority will have submucous clefting or, indeed, frank clefting of the palate.^{8,9} A cleft lip is extraordinarily uncommon in the syndrome. Because palatal weakness affects the ability to close off the nasopharynx, nasal regurgitation is a major problem and contributes to recurrent ear infections. In addition to the palatal defects, the ears can be directly involved in chromosome 22q11.2 deletion syndrome. Common contributors to recurrent ear infections are eustachian tube dysfunction and poor drainage. Most patients will have posterior rotation of the ears, simple helices, or low-set ears, and these features can be a valuable tip to the diagnosis in older patients in whom most of the classic facial dysmorphology has vanished. In addition to the external ear phenotypes, conductive hearing loss has been described, as has sensorineural hearing loss.^{10,11} The mechanism for the hearing loss is not completely understood; however, it has been noted that murine models of chromosome 22q11.2 deletion syndrome have abnormal cochlear development. The last issue that impacts recurrent

TABLE I. Phenotypic features

Feature	% Frequency
Cardiac anomalies	77
Ventriculoseptal defect	21
Tetralogy of Fallot	20
Interrupted aortic arch	12
Truncus arteriosus	6
Immune deficiency	77
T-cell lymphopenia	67
Delayed IgG production	10
Thymic aplasia with absent T cells	<0.1
Hypocalcemia	49
Palatal defects	
Velopharyngeal insufficiency	42
Submucous cleft palate	16
Overt cleft palate	11
Esophageal dysmotility	36
Renal anomalies	36
Feeding and swallowing	35
Dental enamel issues	32
Ophthalmic anomalies	
Posterior embryotoxon	49
Tortuous retinal vessels	34
Strabismus	18
Hearing loss	
Conductive hearing loss	31
Sensorineural hearing loss	2
Spinal abnormalities	
C-spine instability	33
Butterfly vertebrae	11
Behavioral or psychiatric	
Attention deficit hyperactivity disorder	54
Phobias	42
Autism	14
Generalized anxiety	8
Weschler IQ	
Low average	20
Average	18
Structural central nervous system anomalies	
Polymicrogyria	1
Craniosynostosis	1
Cerebellar hypoplasia	<1
Myelomeningocele	<1

upper respiratory tract infections is the aberrant feeding pattern that is seen with high frequency. Patients have poor coordination of the pharyngeal muscles and esophageal muscles, which leads to a disregulated swallow mechanism and may well underlie the gastroesophageal reflux, which also is quite common in the syndrome.¹² The combination of palatal weakness and dysfunctional swallowing often means that formula rests in abnormal anatomic locations or regurgitates into the eustachian tube or sinuses. The high caloric density of formula provides nutrition for bacteria and is thought to contribute to recurrent upper respiratory tract infections.

The International 22q11.2 Deletion Syndrome Consortium has developed a roadmap for the clinical management of

TABLE II. Key components in the immune evaluation of patients with DiGeorge syndrome*

Newborn	
Complete blood cell count with differential.	
Immunophenotyping of T, B, and natural killer cells (CD3, CD4, CD8, CD19 or CD20, and CD56/16, respectively); this is to rule out complete DiGeorge syndrome with absent T-cells.	
If T-cell counts are low, lymphocyte mitogen proliferation assay can be considered.	
Other considerations: cardiac and palatal evaluations, ionized calcium, PTH (parathyroid hormone) and TSH (thyroid stimulating hormone).	
1 year of age	
Repeated immunophenotyping to determine the safety of live viral vaccine administration; avoid if CD4 ⁺ T-cell count is <400 cells.†	
When T-cell counts are low, proliferation assay would be appropriate; quantitative immunoglobulin levels and vaccine antibody titers to assess the humoral arm of the immune system.	
Other considerations: developmental, feeding, and behavioral problems.	
Adult	
Monitor T-cell counts and immunoglobulin levels as indicated based on clinical infection history as well as previous testing results.	
Other considerations: psychiatric, behavioral, and cognitive problems.	

*Individual management of patients with DiGeorge syndrome is essential; the evidence for these time-point guidelines is minimal, and local patterns of practice varies.

†Data from references 35 and 36.

patients.¹³ In addition, it has provided valuable guidelines on specific cautions related to the syndrome. These guidelines acknowledge that the management of patients changes over time. Successful correction of the heart defect renders this much less of an issue as the child ages. Similarly, although speech is commonly delayed in the syndrome, once the child begins to speak, he or she often exhibits voluble speech and good social interactions, which renders the speech concerns less of an issue with age. The Consortium document highlights the many unknowns as well. One of the complex long-term issues in this patient population is the challenge of psychiatric and behavioral problems as the child ages. In the younger age groups, it is clear that patients respond to typical medications for anxiety and attention deficit hyperactivity disorder. However, treatment of teenage-onset schizophrenia and other psychiatric disorders has unfortunately been disappointing. The roadmap for evaluation and the international consensus document provides a useful approach to multidisciplinary patient care, particularly for physicians who are acting as coordinators.

THE IMMUNE DEFICIENCY

The basis for the phenotype of chromosome 22q11.2 deletion syndrome is the abnormal development of the third pharyngeal pouch. It can result in agenesis or hypoplasia of the parathyroid glands and the thymus. In very few patients, <1% with chromosome 22q11.2 deletion syndrome, the thymus and the T cells are absent, and this is referred to as complete DiGeorge syndrome. In 75% of patients, the immune system is affected to some degree, which leaves approximately 20% of patients with normal T-cell counts.⁷ Interestingly, the severity of the other clinical phenotypes appears to be unrelated to the immunologic phenotype.¹⁴ Table II illustrates the key components in the evaluation of the immune system in patients with 22q11.2 deletion syndrome. However, the evaluation should be appropriately adjusted to each individual patient.

The immune deficiency in chromosome 22q11.2 deletion syndrome is traditionally thought to result from the thymus hypoplasia, with B- and natural killer-cell numbers most commonly being normal. Thymus size does not predict T-cell counts, likely due to ectopic thymus tissue,¹⁵ and can range from absent to completely normal. Despite low-for-age T-cell counts in most patients in infancy, this typically improves in the first year of life.¹⁶⁻²² After that age, the normal decline in T-cell counts, seen in the general population, is slower in the patients, which often results in normal-for-age T-cell counts in adulthood. It is believed that this rise in T-cell counts in infancy and normalization in adult patients reflects homeostatic expansion of existing T cells rather than generation of new cells. This is supported by expression of advanced maturation markers on T cells, shorter telomeres, even in naive T cells, and fewer T-cell receptor excision circles in patients compared with controls.²³⁻²⁶ In concordance with this, the T-cell repertoire has decreased diversity (oligoclonal), and spontaneous apoptosis is increased within the T-cell compartment.²⁵⁻²⁸ Oligoclonality has been demonstrated both by spectra-typing as well as by VDJ (variable, diversity, and joining) region sequencing.^{25,26}

Despite the advanced maturation of the T-cell repertoire in patients with 22q11.2 deletion syndrome, T-cell proliferation is often normal, which likely explains why the patients do much better clinically than patients with comparable T-cell counts who have HIV,^{16-18,20,29,30} which suggests that, despite poor thymic output of T cells, antiviral defenses and B-cell help by existing T cells is not greatly impaired, and this is supported by the fact that opportunistic infections are rare.³¹ Other studies, however, describe decreased T-cell responses and proliferation.^{25,26,28,32} In line with the latter, recurrent sinusitis, otitis, and lower airway infections are seen in one-fourth to one-third of adults and children >9 years of age with 22q11.2 deletion syndrome. However, for most patients, live viral vaccines can be safely administered.³³⁻³⁶ Prolonged viral infections are common, and likely abnormal palatal anatomy contributes to risk of upper respiratory bacterial superinfections,¹⁷ which could explain why the frequency of infection and T-cell counts do not correlate well in these patients.¹⁴

Care is needed in the approach to patients with rare complete DiGeorge syndrome who have true thymus aplasia and absence of T cells, due to their severe immune compromise. This group of patients can be defined by <50 T cells/mm³ and/or <50 naive (CD45RA⁺/CD62L⁺ T cells/mm³).^{37,38} These patients need protection from infection and blood products. Both anti-pneumocystis and antifungal prophylaxis should be promptly initiated and immunoglobulin replacement therapy begun. Live viral vaccines should be avoided, although RSV (respiratory syncytial virus) prophylaxis is provided. Indeed, results of studies indicate that live viral vaccines should be strictly avoided in all those with severe T-cell compromise and CD4⁺ T-cell counts of <400 cells/mm³,³⁴⁻³⁶ because vaccine-related infections have been described in such patients.³⁹ Blood products can induce graft-vs-host disease when T cells are absent, and this is usually fatal.⁴⁰ Many patients with 22q11.2 deletion syndrome require cardiac surgery before their immune status is known, and thus these patients should receive cytomegalovirus negative and irradiated blood products.^{13,40} Complete DiGeorge syndrome can present in infants, as described earlier, with absent thymus and T cells or with an atypical phenotype that can be considered a subgroup of Omenn syndrome, with low-to-high

T-cell counts, erythroderma, lymphadenopathy, and hepatosplenomegaly.^{37,41,42} The T cells in these patients are predominantly or exclusively of a memory phenotype (CD4⁺/CD45RO⁺) and show an oligoclonal T-cell receptor repertoire,^{37,43} and thus maternal engraftment needs to be excluded. These T cells have expanded from a few cells, and, despite often high T-cell counts, these T cells are quite dysfunctional, and the patients should be approached as having severe combined immunodeficiency as other patients with complete DiGeorge syndrome.

Although chromosome 22q11.2 deletion syndrome is typically thought to be a T-cell immune deficiency and most patients have normal humoral immunity, there is a growing body of evidence that indicates a functional B-cell defect and hypogammaglobulinemia in some patients,^{44,45} which could be especially important because the adult population with 22q11.2 deletion syndrome grows with improved therapy for cardiac disease, the main mortality impact factor.⁴⁶ The defect appears to be similar to what is seen in common variable immunodeficiency and to be associated with more-severe infections in the affected patients.^{18,23,32,44} In addition, isolated IgA and IgM deficiencies have been described, and, in 1 study, the incidence of specific antibody deficiency was almost 50%.^{23,47,48} A recent review showed that 3% of 850 patients with 22q11.2 deletion syndrome were receiving immunoglobulin replacement therapy and that 6% over the age of 3 years had hypogammaglobulinemia.⁴⁵ There have been reports of patients with 22q11.2 deletion syndrome having delayed B-cell maturation with reduced numbers of both naive and unswitched memory B cells (CD27⁺/IgM⁺/IgD⁺) as well as reduced peripheral class-switched memory B cells (CD27⁺/IgM⁻/IgD⁻).^{21,23,32,49} How common and significant this defect in the humoral arm of the immune system is in 22q11.2 deletion syndrome remains to be elucidated.

TRANSPLANTATION

Immune system reconstitution is essential for patients with complete DiGeorge syndrome and can be accomplished by 2 means, by thymus tissue transplantation or, alternatively, by a fully matched peripheral blood T-cell transplantation.⁵⁰ As expected, hematopoietic cell transplantation does not result in ongoing T-cell lymphopoiesis with the majority having persistent CD4⁺ T-cell lymphopenia and a skewed T-cell receptor repertoire.^{51,52} Although it is not clear if the lack of lymphopoiesis in this setting affects long-term survival, the overall survival of 41%-48% does not compare favorably with hematopoietic transplantation for other forms of severe combined immune deficiency.^{52,53} The main causes of mortality appear to be surgical conditions and graft-vs-host disease.⁵¹ The other alternative, thymus transplantation, refers to implantation of cultured thymus donor tissue in thin slices into the quadriceps muscle after mature T cells have been eliminated to reduce the risk of graft-vs-host disease.^{54,55} Thymopoiesis can be observed in biopsies of the transplanted tissue within 2 months of transplantation and naive T cells are detected in peripheral blood at 3-5 months after transplantation.^{56,57} Although the T-cell counts are <10th percentile for age, the cells show proliferation in response to mitogens and diversity in the T-cell receptor variable β -chain by spectra-typing.^{38,55,58} Survival is fair, at 72%, with survivors appearing to be protected from infections.^{38,57}

Development of immunoglobulin production and some vaccine responses have been demonstrated after transplantation, although responses were not as robust as in controls.^{38,57} Importantly, the thymus implant involutes with time, and follow-up studies will reveal the long-term outcome of these patients. Few patients with complete DiGeorge syndrome and maternal engraftment have received thymus transplantations but they, unlike other patients with thymus transplantations, have been treated with antithymocyte globulin and calcineurin inhibitors to prevent the pathologic T-cell clones from engrafting, but they also appear to have favorable immune outcomes. The most-frequent adverse outcomes after thymus transplantation are infections, typically before naive T-cell development, and autoimmune disease. The most-common autoimmune disease seen has been thyroid disease (22%).⁵⁹ Autoimmune cytopenias have been seen in 15%, and there was a case report of severe posttransplantation enteritis and/or colitis, with subsequent lethal fungal pneumonia.³⁸ The success of thymus transplantation is surprising because it is accomplished without HLA matching, although the thymus is known to be the site of both negative and positive selections of T cells. Negative selection presumably is intact due to the migration of recipient's CD83⁺ dendritic cells from marrow to the implanted thymus.⁵⁷ However, positive selection to ensure recognition of self major histocompatibility complex by T cells would be predicted to become restricted to the thymus donor major histocompatibility complex antigens. This does not correlate with successful reconstitution of T-cell function in the recipient, and the mechanism remains undefined.⁵⁷ Interestingly, analysis of recent data indicates that progenitor cells exist in the thymus, which allows development of both cortical and medullary epithelia after transplantation.⁶⁰

ALLERGIC AND AUTOIMMUNE DISEASE

Allergic disease appears to be more common in patients with chromosome 22q11.2 deletion syndrome compared with the general population and could contribute to the increased frequency of upper respiratory infections,⁶¹ which may be explained by preferential differentiation of Th2 cells in the homeostatic expansion of T cells as has been observed in mice.⁶² Autoimmune disease is seen in approximately 10% of patients with deletion syndrome.¹⁷ Most commonly reported are hematologic autoimmune diseases such as idiopathic thrombocytopenia purpura, hemolytic anemia, thyroid disease, and juvenile idiopathic arthritis.^{17,63-69} In addition, there are reports that indicate that celiac disease is more common in patients with 22q11.2 deletion syndrome than in the general population.⁷⁰ There appears to be an increased risk of autoimmune diseases in general rather than a risk of a specific autoimmune disease.^{44,71} The pathophysiology for this is unclear but is thought to be related to fewer regulatory T cells and selection for self-reactive T cells with homeostatic expansion.^{72,73}

THE OPENING VIGNETTE

The immunologic evaluation of the 2-year-old boy described in the abstract demonstrated a low-for-age T-cell count (CD3), at 848 cells/mm³, with a CD4⁺ T-cell count of 573 cells/mm³. His naive-to-memory T-cell ratio was advanced, which had a higher proportion of memory T cells than expected for his age, but his quantitative immunoglobulin levels were normal as well as were antibody titers to pneumococcal, diphtheria, and tetanus

vaccines. He was cleared to receive live viral vaccines and was treated with antibiotic prophylaxis, with a marked reduction of sinopulmonary infections. These findings are extremely typical for toddlers with chromosome 22q11.2 deletion syndrome. As described, the heterogeneity in this syndrome is extreme, and each patient will require individualized care. Not all patients respond to prophylactic antibiotics. Maintaining an open mind about nonimmunologic contributors to infection and assessing other organ system effects is critical to ensuring that each patient reaches his or her potential (Table II).

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